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Distant metastasis in colorectal cancer is a risk factor for anastomotic leakage

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Running head: Stage IV colorectal cancer & anastomotic leaks

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Synopsis: Patients with resection for stage IV colorectal cancer have an increased anastomotic leak rate.

Abstract

Purpose: To investigate if metastatic colorectal cancer (UICC stage IV disease) represents a risk factor for anastomotic leakage after colorectal surgery without major hepatic resection.

Methods: This retrospective cohort study is based on an existing prospective colorectal database with all consecutive colorectal resections done at the authors' institution from 07/2002 to 07/2012 (n=2104). All patients with colorectal resection and primary anastomosis for colorectal cancer were identified (n=500). A temporary loop ileostomy was constructed in low rectal anastomosis up to 6 cm from anal verge (n=128 cases; 26%). Routine contrast enema was done at the occasion of other prospective studies (n=254). UICC stage IV disease was present in n=94 patients (19%), while n=406 (81%) had UICC stage I to III disease.

Results: The overall anastomotic leak rate was 2.6% (13/500), 2.2% (11/500) for both clinical and radiological leaks, and 0.8% (2/254) for radiological leaks only. N=4 were managed conservatively, and n=9 (1.8%) required revision laparotomy. In the case of UICC stage IV disease, the anastomotic leak rate was 6.3% (6/94); in the case of UICC stage I to III disease the leak rate was 1.7% (7/406). UICC stage IV disease (odds ratio 4.4, 95% confidence interval 1.3 - 14.4, p=0.015) and diabetes (odds ratio 5.7, 95% confidence interval 1.7 - 18.7, p=0.004) remained independent risk factors for anastomotic leakage after colorectal surgery.

Conclusions: Patients with stage IV colorectal cancer have an increased anastomotic leak rate after colorectal surgery. Whether this is due to impaired immune system remains speculation.

Introduction

One in five patient with diagnosed colorectal cancer has synchronous liver metastasis and only a minority qualifies for curative liver resection [1]. Different treatment strategies in the palliative and in the curative setting are under debate [2-8]. However, surprisingly little is known on the specific risks of colorectal surgery in patients with metastatic colorectal cancer.

We aimed to determine if metastatic colorectal cancer (UICC stage IV disease) itself represents a risk factor for anastomotic leakage after colonic or rectal anastomosis without major hepatic resection and to compare it to other known risk factors of anastomotic leakage.

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This retrospective cohort study is based on an existing prospective colorectal database with all consecutive colorectal resections done at the authors' institution from 07/2002 to 07/2012 (n=2104). As different hospitals are located near the authors' institution the study is not population based. Patients with colorectal resections without colonic or rectal anastomosis (n=229) were excluded. From the remaining n=1875 patients, those with the following procedures were excluded: reversal of hartmann's procedure (n=70), redo of anastomosis for anastomotic leak (n=7), colon resection and primary anastomosis for the following diseases: diverticular disease (n=661), colorectal adenoma (n=111), rectal prolapse (n=122), non-colorectal cancer (n=101), complicated appendicitis (n=63), chronic inflammatory bowel disease (n=58), ischemic or infectious colitis (n=44), iatrogenic or traumatic colon perforation (n=37), non-malignant large bowel obstruction (including anastomotic stenosis, radiation injuries, incarcerated hernia n=30), slow-transit constipation (n=22), volvulus (n=11), Ogilvie's syndrome with severe colonic

damage (n=10), colonic bleeding (n=22), and other reasons (n=6). Finally, n=500 patients with colorectal resection and primary anastomosis for colorectal cancer were included in the study.

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A temporary loop ileostomy was always constructed in low rectal anastomosis up to 6 cm from anal verge (n=128 cases; 26%).

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Extravasation of water-soluble contrast medium in conventional contrast enema or CT scan, abscesses near the colonic or rectal anastomosis without extravasation of contrast medium, and anastomotic leaks diagnosed during surgical re-intervention in presence of obvious signs of an anastomotic leak such as fecal abdominal drainage were accounted as an anastomotic leak. The patients were observed clinically and by routine inflammation markers during hospitalization for several days. However, in the case of unexpected postoperative course after sending home the patients, they reliably were sent back to the present surgical unit for further treatment.

Routine contrast enema was done at the occasion of other prospective studies (n=254), especially in all patients with temporary loop ileostomy (n=131). In the remaining patients (n=246) contrast enema was only done in the case of suspicion of an anastomotic leak.

UICC stage IV disease was present in n=94 patients (19%), while n=406 (81%) had UICC stage I to III disease. An overview of the study methodology is shown in Figure 1.

Statistics: Results are expressed as median and range or mean and standard deviation whenever appropriate. Categorical data was analyzed with the two-sided Fisher's exact test and Pearson's Chi Square if the contingency table was larger than 2x2. Continuous data was analyzed with the Wilcoxon rank sum test. Multivariate analyses were done by logistic regression. P-values < 0.05 were considered statistically significant.

Ethics statement: The present study is a retrospective observational study without any experimental protocols and thus no potential harm for patients.

Results

The only significant difference in the patients' characteristics between patients with stage I-III to patients with stage IV colorectal cancer was the ASA (American Society of Anesthesiologists) score as shown in table 1. The distribution of metastases in patients with metastatic disease (n=94) was: 49% (n=46) liver only, 3% (n=3) lung only, 3% (n=3) peritoneal only, 3% (n=3) retroperitoneal only, 12% (n=11) liver and lung only, 12% (n=11) peritoneal and liver only, 1% (n=1) retroperitoneal and lung only, and 17% (n=16) multiorgan disease.

Patients with metastatic disease were treated with a curative intention in 42.5% (n=40), while 41.5% (n=39) had a planned palliative therapy and the remaining 16% (n=15) had palliative best supportive care due to their poor general state.

The anastomotic leaks were diagnosed on median postoperative day 6 (range 1-15). The overall anastomotic leak rate was 2.6% (13/500). Two of these thirteen anastomotic leaks were diagnosed by routine contrast enema and remained subclinical i.e. without symptoms, two were managed conservatively, and nine required revision laparotomy.

It is noteworthy that three of the six patients with stage IV colorectal cancer who had anastomotic leakage were in a palliative setting.

The analyzed and detected risk factors for the development of an anastomotic leak after resection of colon or rectal cancer (univariate) are shown in Table 2. The results of the multivariate analyses comparing the detected risk factors for the development of an anastomotic leak after resection of colon or rectal cancer are shown in Table 3; stage IV colorectal cancer and diabetes remained statistically significant risk factors for the development of an anastomotic leak, while male gender and resection of left-sided colon cancer or rectal cancer did not.

The leak rate of patients with and without UICC stage IV colorectal cancer is depicted in Figure 2. The leak rate was 9% (6/63) in patients with diabetes mellitus and 1.6% (7/437) without.

Subgroup analyses: colon cancer

From n=339 patients with colon cancer, n=10 had anastomotic leakage (2.9%). With respect to the type of surgery the leak rates were as following: left hemicolectomy 6.7% (8/137); subtotal colectomy (1/31); transverse resection (0/5), right hemicolectomy 0.6% (1/166).

Univariate analysis revealed that stage IV disease (p=0.006), left colon cancer (p=0.010), and male gender (p=0.023) were statistically significant predictors of anastomotic leakage after resection of colon cancer, while the other analyzed factors were not. Multivariate analyses with the detected significant predictors of anastomotic leakage showed that stage IV disease (p=0.003, Odds ratio 7.6 [95% confidence interval: 2.0 – 29.4]), left-sided colon cancer (p=0.025, Odds ratio 11.1 [95% confidence interval: 1.3 – 91.8]), and male gender (p=0.045, Odds ratio 8.7 [95%

confidence interval: 1.0 – 71.5]) remained independent statistically significant predictors of anastomotic leakage after resection of colon cancer.

Subgroup analyses: rectal cancer

From n=161 patients with rectal cancer, n=3 patients had anastomotic leakage (1.9%). In patients with high anterior recto-sigmoid resection with partial mesorectal excision without loop ileostomy for cancer of the upper third of the rectum (n=30) no leak occured, while in those patients with low anterior rectal resection with loop ileostomy for cancer of the lower two thirds of the rectum (n=128) or with high anterior recto-sigmoid resection with loop ileostomy (n=3) the leak rate was 2.3% (3/131).

Univariate analysis revealed that diabetes (p=0.001) and a lower preoperative hemoglobin value (p=0.023) were statistically significant predictors of anastomotic leakage, while the other analyzed factors were not. Multivariate analyses with the two detected significant predictors of anastomotic leakage showed that diabetes (p<0.001 Odds ratio 7.7E8 [95% confidence interval: 11.9E3 – 5.0E13]) remained a statistically significant predictor of anastomotic leakage while a lower preoperative hemoglobin value (p=0.143 Odds ratio 0.5 [95% confidence interval: 0.2 – 1.3]) did not.

Discussion

Surprisingly little is known on the risks of colorectal surgery in patients with metastatic colorectal cancer. This study shows that metastatic colorectal cancer (UICC stage IV disease) itself is a risk factor for anastomotic leakage after colorectal surgery without major hepatic resection. Is this finding plausible?

First it is known that liver metastasis leads to an altered immune response [9,10]. Immunosuppression as induced by steroids is a well-known risk factor for the development of an anastomotic leak after colorectal surgery [11].

Second up to 65% of the patients with grade IV colorectal cancer have malnutrition [12], and patients with malnutrition also have an altered immune response with an exaggerated Interleukin-6 and a suppressed Interleukin-1 response [13,14]. A low level of Interleukin-1-receptor-antagonist is a known risk factor for adverse outcome after colorectal surgery [15].

Besides metastatic colorectal cancer as a risk factor for anastomotic leakage, diabetes was identified as a second risk factor for anastomotic leakage. Diabetes is a known risk factor for delayed wound healing [18] and thus it can be assumed to be a risk factor for anastomotic leakage after colorectal surgery as well. Indeed some studies identified diabetes as a risk factor for anastomotic leakage after colorectal surgery [19,20], while others did not [21,22]. Subgroup analyses revealed that in this study diabetes only remained a risk factor for anastomotic leakage in patients with rectal cancer. However, further research is needed to confirm if diabetes is a risk factor for anastomotic leakage after colorectal surgery or not.

Subgroup analyses of those patients with resection of left-sided colon cancer had a significant higher leakage rate than those with right-sided colorectal cancer. This is known from literature[16,17]. We draw the conclusion that the construction of a temporary loop ileostomy should be considered in patients with left-sided stage IV colon cancer.

Subgroup analyses also identified male gender as a significant risk factor for anastomotic leakage in patients with resection for colon cancer, as known from literature[23].

Limitations

The treatment policy for patients with stage IV colorectal cancer was to do the colorectal resection if feasible and safe. As mentioned above the study is not population based. Thus a patient selection bias with a selection of those patients in a better general state is possible. However, if more patients in a worse general state with an expected higher leakage rate would have been included, it can be assumed that stage IV disease would have turned out to be an even stronger predictor of anastomotic leakage.

As only about half of the patients were investigated by routine radiology (n=254) few subclinical anastomotic leaks could have been missed in those patients who did not have routine radiology (n=246). As one of the two patients with a subclinical leak had stage I cancer and the other had stage IV cancer a bias is not expected.

This study has a retrospective design. Thus, a further bias cannot be excluded. However, a bias was minimized by including all consecutive patients registered in a prospective database who had colorectal resection at the same institution in a predefined period of ten years.

To confirm the results of this study and to prove the value of a routine temporary loop ileostomy in patients with left-sided stage IV colon cancer a prospective randomized trial is required.

Conclusion

Patients with stage IV colorectal cancer have an increased leak rate after colonic or rectal anastomosis. Whether this is due to impaired immune system remains speculation.

Table 1 Patients' characteristics

Risk factor	Stage I - III colorectal cancer (n=406)	Stage IV colorectal cancer (n=94)	p-value
Mean age (SD)	70 (12) years	69 (12) years	0.190
Male gender	n=237/406	n=53/94	0.729
Median ASA Score (Range)	2 (1-5)	3 (1-4)	0.012
Cardiac comorbidities	n=204/356 (57%)	n=55/85 (65%)	0.372
Vascular comorbidities	n=41/342 (12%)	n=6/85 (7%)	0.327
Diabetes	n=54/356 (15%)	n=9/85 (11%)	0.388
Pulmonary comorbidities	n=55/356 (15%)	n=18/85 (21%)	0.198
Tobacco abuse	n=48/356 (13%)	n=15/85 (18%)	0.307
Obesity	n=195/356 (55%)	n=54/85 (64%)	0.180
Dementia	n=12/355 (3%)	n=0/85 (0%)	0.135
Immunosuppressive drugs	n=6/352 (2%)	n=2/85 (2%)	0.656
Non-steroidal anti-inflammatory drugs	n=62/352 (18%)	n=13/85 (15%)	0.749
Presence of peritonitis	n=22/329 (7%)	n=5/85 (6%)	1.000
Large bowel obstruction	n=37/351 (11%)	n=10/85 (12%)	0.700
Urgent surgery	n=49/351 (14%)	n=12/85 (15%)	1.000

SD: standard deviation, ASA: American Society of Anesthesiologists

Table 2 Results of the univariate analyses of the risk factors of anastomotic leakage after colorectal surgery for colorectal cancer.

Risk factor	Anastomotic leak (n=13)	No anastomotic leak (n=487)	p-value
Mean age (SD)	73 (8) years	70 (12) years	0.516
Male gender	12/13	278/487 (57%)	0.010
Median ASA Score (Range)	2 (1-3)	2 (1-5)	0.657
Cardiac comorbidities	9/13	250/428 (58%)	0.584
Vascular comorbidities	2/13	45/428 (11%)	0.638
Diabetes	6/13	57/428 (13%)	0.005
Pulmonary comorbidities	1/13	72/428 (17%)	0.704
Tobacco abuse	2/13	61/428 (14%)	1.000
Obesity	8/13	241/428 (56%)	0.783
Dementia	0/13	12/427 (3%)	1.000
Immunosuppressive drugs	0/13	8/424 (2%)	1.000
Non-steroidal anti-inflammatory drugs	3/13	72/424 (17%)	0.475
Preoperative radio- and/or chemotherapy	**0/13**	**43/472 (9%)**	**0.617**
Presence of peritonitis	0/13	27/396 (7%)	1.000
Large bowel obstruction	1/13	46/377 (12%)	1.000
Urgent surgery	1/13	60/396 (15%)	0.702
ypT0 or T1 cancer	2/13	52/487 (11%)	

T2 cancer	4/13	73/487 (15%)	
T3 cancer	3/13	245/487 (50%)	
T4 cancer	4/13	117/487 (24%)	0.218
Nodal positive cancer	8/13	219/473 (46%)	0.270
Stage IV colorectal cancer	6/13	88/487 (18%)	0.021
Resection of left-sided colon cancer or rectal cancer	12/13	317/487 (65%)	0.0417
Preoperative mean (SD) white blood cell count (1/10E9)	8.0 (3.5)	7.7 (3.0)	0.629
Preoperative mean (SD) Hemoglobin	12.6 (2.0)	12.8 (2.1)	0.814
Preoperative mean (SD) Sodium	138.5 (2.9)	139.7 (3.1)	0.0935
Preoperative mean (SD) Potassium	4.3 (0.4)	4.1 (0.4)	0.324
Preoperative mean (SD) Creatinine	82.8 (23.8)	79.7 (40.8)	0.328
Preoperative mean (SD) Albumin	38 (4.0)	39.3 (5.5)	0.1872

SD: standard deviation, ASA: American Society of Anesthesiologists

Table 3 Results of the multivariate analyses of the detected risk factors for anastomotic leakage after colorectal surgery for colorectal cancer.

Risk factor	Odds ratio	95%confidence interval	p-value
Diabetes	5.7	1.7 – 18.7	0.004
Stage IV colorectal cancer	4.4	1.3 – 14.4	0.015
Male gender	7.8	1.0 – 62.6	0.052
Resection of left-sided colorectal cancer or rectal cancer	6.7	0.8 – 53.0	0.073

ASA: American Society of Anesthesiologists

Figure 1: Flow diagram of the study methodology

Figure 2: Anastomotic leakage rate in Stage I to III versus Stage IV colorectal cancer

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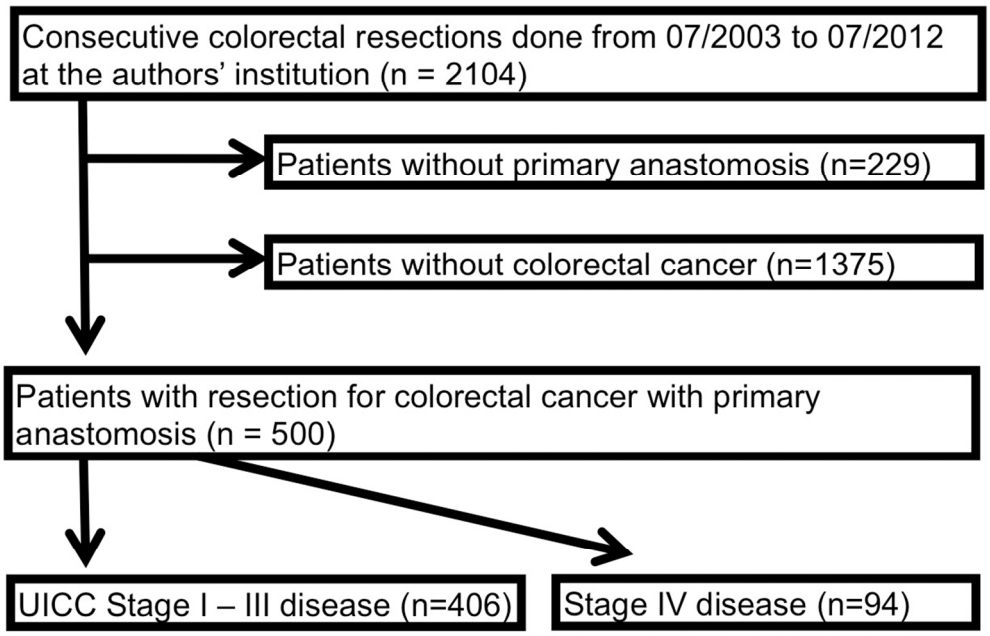

Flow diagram of the study methodology
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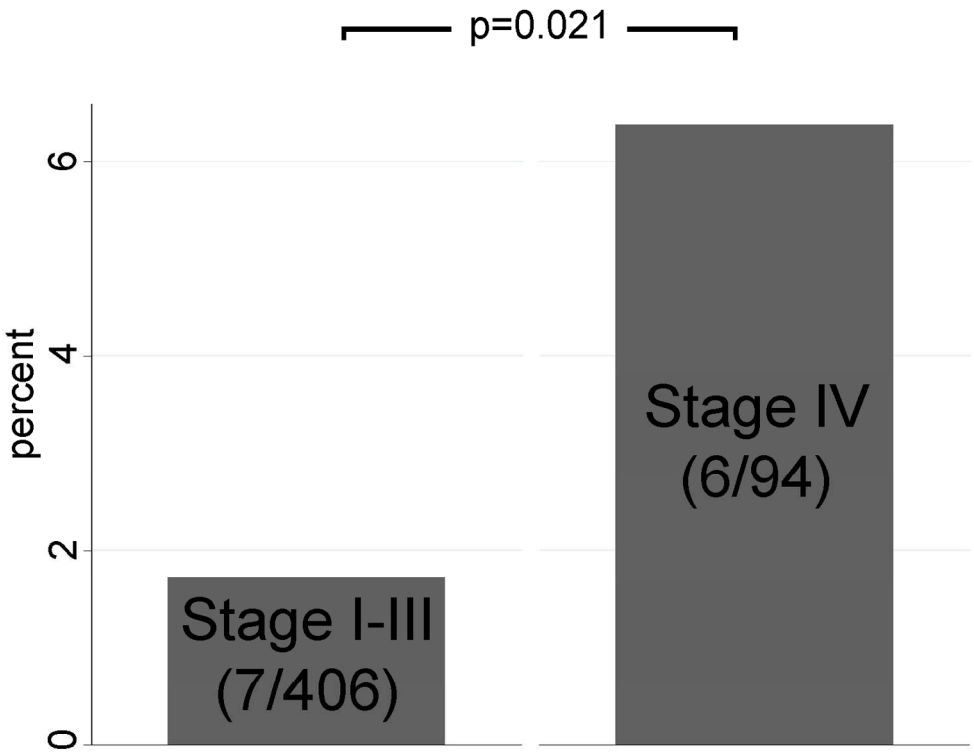

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The only significant difference in the patients' characteristics between patients with stage I-III to patients with stage IV colorectal cancer was the ASA (American Society of Anesthesiologists) score as shown in table 1. The distribution of metastases in patients with metastatic disease (n=94) was: 49% (n=46) liver only, 3% (n=3) lung only, 3% (n=3) peritoneal only, 3% (n=3) retroperitoneal only, 12% (n=11) liver and lung only, 12% (n=11) peritoneal and liver only, 1% (n=1) retroperitoneal and lung only, and 17% (n=16) multiorgan disease.

Patients with metastatic disease were treated with a curative intention in 42.5% (n=40), while 41.5% (n=39) had a planned palliative therapy and the remaining 16% (n=15) had palliative best supportive care due to their poor general state.

The anastomotic leaks were diagnosed on median postoperative day 6 (range 1-15). The overall anastomotic leak rate was 2.6% (13/500). Two of these thirteen anastomotic leaks were diagnosed by routine contrast enema and remained subclinical i.e. without symptoms, two were managed conservatively, and nine required revision laparotomy.

It is noteworthy that three of the six patients with stage IV colorectal cancer who had anastomotic leakage were in a palliative setting.

The analyzed and detected risk factors for the development of an anastomotic leak after resection of colon or rectal cancer (univariate) are shown in Table 2. The results of the multivariate analyses comparing the detected risk factors for the development of an anastomotic leak after resection of colon or rectal cancer are shown in Table 3; stage IV colorectal cancer and diabetes remained statistically significant risk factors for the development of an anastomotic leak, while male gender and resection of left-sided colon cancer or rectal cancer did not.

The leak rate of patients with and without UICC stage IV colorectal cancer is depicted in Figure 2. The leak rate was 9% (6/63) in patients with diabetes mellitus and 1.6% (7/437) without.

Subgroup analyses: colon cancer

From n=339 patients with colon cancer, n=10 had anastomotic leakage (2.9%). With respect to the type of surgery the leak rates were as following: left hemicolectomy 6.7% (8/137); subtotal colectomy (1/31); transverse resection (0/5), right hemicolectomy 0.6% (1/166).

Univariate analysis revealed that stage IV disease (p=0.006), left colon cancer (p=0.010), and male gender (p=0.023) were statistically significant predictors of anastomotic leakage after resection of colon cancer, while the other analyzed factors were not. Multivariate analyses with the detected significant predictors of anastomotic leakage showed that stage IV disease (p=0.003, Odds ratio 7.6 [95% confidence interval: 2.0 – 29.4]), left-sided colon cancer (p=0.025, Odds ratio 11.1 [95% confidence interval: 1.3 – 91.8]), and male gender (p=0.045, Odds ratio 8.7 [95%

confidence interval: 1.0 – 71.5]) remained independent statistically significant predictors of anastomotic leakage after resection of colon cancer.

Subgroup analyses: rectal cancer

From n=161 patients with rectal cancer, n=3 patients had anastomotic leakage (1.9%). In patients with high anterior recto-sigmoid resection with partial mesorectal excision without loop ileostomy for cancer of the upper third of the rectum (n=30) no leak occured, while in those patients with low anterior rectal resection with loop ileostomy for cancer of the lower two thirds of the rectum (n=128) or with high anterior recto-sigmoid resection with loop ileostomy (n=3) the leak rate was 2.3% (3/131).

Univariate analysis revealed that diabetes (p=0.001) and a lower preoperative hemoglobin value (p=0.023) were statistically significant predictors of anastomotic leakage, while the other analyzed factors were not. Multivariate analyses with the two detected significant predictors of anastomotic leakage showed that diabetes (p<0.001 Odds ratio 7.7E8 [95% confidence interval: 11.9E3 – 5.0E13]) remained a statistically significant predictor of anastomotic leakage while a lower preoperative hemoglobin value (p=0.143 Odds ratio 0.5 [95% confidence interval: 0.2 – 1.3]) did not.

Discussion

Surprisingly little is known on the risks of colorectal surgery in patients with metastatic colorectal cancer. This study shows that metastatic colorectal cancer (UICC stage IV disease) itself is a risk factor for anastomotic leakage after colorectal surgery without major hepatic resection. Is this finding plausible?

First it is known that liver metastasis leads to an altered immune response [9,10]. Immunosuppression as induced by steroids is a well-known risk factor for the development of an anastomotic leak after colorectal surgery [11].

Second up to 65% of the patients with grade IV colorectal cancer have malnutrition [12], and patients with malnutrition also have an altered immune response with an exaggerated Interleukin-6 and a suppressed Interleukin-1 response [13,14]. A low level of Interleukin-1-receptor-antagonist is a known risk factor for adverse outcome after colorectal surgery [15].

Besides metastatic colorectal cancer as a risk factor for anastomotic leakage, diabetes was identified as a second risk factor for anastomotic leakage. Diabetes is a known risk factor for delayed wound healing [18] and thus it can be assumed to be a risk factor for anastomotic leakage after colorectal surgery as well. Indeed some studies identified diabetes as a risk factor for anastomotic leakage after colorectal surgery [19,20], while others did not [21,22]. Subgroup analyses revealed that in this study diabetes only remained a risk factor for anastomotic leakage in patients with rectal cancer. However, further research is needed to confirm if diabetes is a risk factor for anastomotic leakage after colorectal surgery or not.

Subgroup analyses of those patients with resection of left-sided colon cancer had a significant higher leakage rate than those with right-sided colorectal cancer. This is known from literature[16,17]. We draw the conclusion that the construction of a temporary loop ileostomy should be considered in patients with left-sided stage IV colon cancer.

Subgroup analyses also identified male gender as a significant risk factor for anastomotic leakage in patients with resection for colon cancer, as known from literature[23].

Limitations

The treatment policy for patients with stage IV colorectal cancer was to do the colorectal resection if feasible and safe. As mentioned above the study is not population based. Thus a patient selection bias with a selection of those patients in a better general state is possible. However, if more patients in a worse general state with an expected higher leakage rate would have been included, it can be assumed that stage IV disease would have turned out to be an even stronger predictor of anastomotic leakage.

As only about half of the patients were investigated by routine radiology (n=254) few subclinical anastomotic leaks could have been missed in those patients who did not have routine radiology (n=246). As one of the two patients with a subclinical leak had stage I cancer and the other had stage IV cancer a bias is not expected.

This study has a retrospective design. Thus, a further bias cannot be excluded. However, a bias was minimized by including all consecutive patients registered in a prospective database who had colorectal resection at the same institution in a predefined period of ten years.

To confirm the results of this study and to prove the value of a routine temporary loop ileostomy in patients with left-sided stage IV colon cancer a prospective randomized trial is required.

Conclusion

Patients with stage IV colorectal cancer have an increased leak rate after colonic or rectal anastomosis. Whether this is due to impaired immune system remains speculation.

Table 1 Patients' characteristics

Risk factor	Stage I - III colorectal cancer (n=406)	Stage IV colorectal cancer (n=94)	p-value
Mean age (SD)	70 (12) years	69 (12) years	0.190
Male gender	n=237/406	n=53/94	0.729
Median ASA Score (Range)	2 (1-5)	3 (1-4)	0.012
Cardiac comorbidities	n=204/356 (57%)	n=55/85 (65%)	0.372
Vascular comorbidities	n=41/342 (12%)	n=6/85 (7%)	0.327
Diabetes	n=54/356 (15%)	n=9/85 (11%)	0.388
Pulmonary comorbidities	n=55/356 (15%)	n=18/85 (21%)	0.198
Tobacco abuse	n=48/356 (13%)	n=15/85 (18%)	0.307
Obesity	n=195/356 (55%)	n=54/85 (64%)	0.180
Dementia	n=12/355 (3%)	n=0/85 (0%)	0.135
Immunosuppressive drugs	n=6/352 (2%)	n=2/85 (2%)	0.656
Non-steroidal anti-inflammatory drugs	n=62/352 (18%)	n=13/85 (15%)	0.749
Presence of peritonitis	n=22/329 (7%)	n=5/85 (6%)	1.000
Large bowel obstruction	n=37/351 (11%)	n=10/85 (12%)	0.700
Urgent surgery	n=49/351 (14%)	n=12/85 (15%)	1.000

SD: standard deviation, ASA: American Society of Anesthesiologists

Table 2 Results of the univariate analyses of the risk factors of anastomotic leakage after colorectal surgery for colorectal cancer.

Risk factor	Anastomotic leak (n=13)	No anastomotic leak (n=487)	p-value
Mean age (SD)	73 (8) years	70 (12) years	0.516
Male gender	12/13	278/487 (57%)	0.010
Median ASA Score (Range)	2 (1-3)	2 (1-5)	0.657
Cardiac comorbidities	9/13	250/428 (58%)	0.584
Vascular comorbidities	2/13	45/428 (11%)	0.638
Diabetes	6/13	57/428 (13%)	0.005
Pulmonary comorbidities	1/13	72/428 (17%)	0.704
Tobacco abuse	2/13	61/428 (14%)	1.000
Obesity	8/13	241/428 (56%)	0.783
Dementia	0/13	12/427 (3%)	1.000
Immunosuppressive drugs	0/13	8/424 (2%)	1.000
Non-steroidal anti-inflammatory drugs	3/13	72/424 (17%)	0.475
Preoperative radio- and/or chemotherapy	**0/13**	**43/472 (9%)**	**0.617**
Presence of peritonitis	0/13	27/396 (7%)	1.000
Large bowel obstruction	1/13	46/377 (12%)	1.000
Urgent surgery	1/13	60/396 (15%)	0.702
ypT0 or T1 cancer	2/13	52/487 (11%)	

T2 cancer	4/13	73/487 (15%)	
T3 cancer	3/13	245/487 (50%)	
T4 cancer	4/13	117/487 (24%)	0.218
Nodal positive cancer	8/13	219/473 (46%)	0.270
Stage IV colorectal cancer	6/13	88/487 (18%)	0.021
Resection of left-sided colon cancer or rectal cancer	12/13	317/487 (65%)	0.0417
Preoperative mean (SD) white blood cell count (1/10E9)	8.0 (3.5)	7.7 (3.0)	0.629
Preoperative mean (SD) Hemoglobin	12.6 (2.0)	12.8 (2.1)	0.814
Preoperative mean (SD) Sodium	138.5 (2.9)	139.7 (3.1)	0.0935
Preoperative mean (SD) Potassium	4.3 (0.4)	4.1 (0.4)	0.324
Preoperative mean (SD) Creatinine	82.8 (23.8)	79.7 (40.8)	0.328
Preoperative mean (SD) Albumin	38 (4.0)	39.3 (5.5)	0.1872

SD: standard deviation, ASA: American Society of Anesthesiologists

Table 3 Results of the multivariate analyses of the detected risk factors for anastomotic leakage after colorectal surgery for colorectal cancer.

Risk factor	Odds ratio	95%confidence interval	p-value
Diabetes	5.7	1.7 – 18.7	0.004
Stage IV colorectal cancer	4.4	1.3 – 14.4	0.015
Male gender	7.8	1.0 – 62.6	0.052
Resection of left-sided colorectal cancer or rectal cancer	6.7	0.8 – 53.0	0.073

ASA: American Society of Anesthesiologists

Figure 1: Flow diagram of the study methodology

Figure 2: Anastomotic leakage rate in Stage I to III versus Stage IV colorectal cancer

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